Regulatory Requirements for Clinical Development of Monoclonal Antibody Therapies for BEID

Biodefense and Emerging Infectious Diseases

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Outline

- Background
  - Laws and regulations, Transfer of certain biologics to CDER
- Examples from drug development
  - Ciprofloxacin, Doxycycline/Penicillin G, Levofloxacin
- Monoclonal antibodies
  - Points to consider, Clinical development, Animal rule

Background

- Biologics statutes
  - Public Health Service (PHS) Act (1944)
    - Section 351 -- Licensure of biological establishments and products
  - Food, Drug, and Cosmetic Act (FDCA) (1938, 1962)
    - Interprets “biological products” to also be “drugs”
    - FDCA applies to biological products, except no drug application required

Background

- Biologics regulations
  - Title 21, Code of Federal Regulations (CFR) Subchapter F - Biologics
    - Part 600 – General
    - Part 601 – Licensure
    - Part 610 – Standards
    - Part 312 – IND application
    - Part 50 – Protection of Human Subjects
    - Part 56 – IRBs
    - Part 58 – GLP for nonclinical lab studies (see Animal Rule)

Change in Regulatory Responsibility - Transfer of Certain Biologics

- June 30, 2003, responsibilities for most therapeutic biologics transferred from OTRR to OND and OPS
- October 1, 2003, reorganization to ODEVI
- October 1, 2005, integration of therapeutic proteins into OND review offices/divisions

OTRR-Office of Therapeutics Research and Review, CBER

OND – Office of New Drugs, CDER; OPS-Office of Pharmaceutical Science, CDER

FR Notice of final rule March 24, 2005

Biologics transferred to CDER

- Monoclonal antibodies for in-vivo use
- Proteins intended for therapeutic use
  - including cytokines, enzymes, novel proteins (except those specifically assigned to CBER, e.g. vaccines and blood products)
- Immunomodulators
  - (nonvaccine and nonallergeneic products intended to treat disease by inhibiting or modifying a preexisting immune response)
- Growth factors, cytokines and monoclonal antibodies
  - intended to mobilize, stimulate , decrease or otherwise alter the production of hematopoietic cells in vivo.

Biologics remaining in CBER

- Cellular products
- Allergenic extracts
- Antitoxins, antivenins, venoms
- Vaccines
- Blood, blood components, plasma derived products

FR March 24, 2005 (p14978)

- "This consolidation initiative was undertaken to provide greater opportunities to further develop and coordinate scientific and regulatory activities between CBER and CDER... for human drugs and biologics."

Examples from Drug Development for Biodefense

Ciprofloxacin

Doxycycline/ Penicillin G procaine

Levofloxacin

Drug Experience - ciprofloxacin

- Approved for post-exposure prophylaxis in August 30, 2000
  - **Inhalational anthrax** (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis.* Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication. (See also, INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION).
  - Adult: 500 mg PO 12 h for 60 Days
    - or 400mg IV q12
  - Pediatric:15 mg/kg PO per dose q12h for 60 Days
    - Or 10 mg/kg per dose IV

Ciprofloxacin

- Relevant background information
  - FQ antimicrobial marketed since 1987
  - Approved for multiple indications
    - Including infections involving reticuloendothelial system (macrophage/monocyte)
  - Millions of human exposures
  - Safety for 60 days or longer in adults and pediatric patients (CF, etc)

Ciprofloxacin (cont)

- Specific for PEP indication
  - In vitro susceptibility of *B anthracis*
  - Clinical pharmacology
    - Human adult
    - Human pediatric
    - Non human primate
  - Non human primate study
    - Friedlander 1993*

*Friedlander, A. M. et al., ``Postexposure Prophylaxis Against Experimental Inhalation Anthrax,'' Journal of Infectious Diseases, 167:1239-1243, 1993.

Ciprofloxacin PEP approval and labeling

- Advisory Committee meeting July 28, 2000
- Adequate safety for adult and pediatric up to 60 days
- Efficacy extrapolated from NHP
- Approved under 21 CFR Subpart H, 314.510 (vs 21 CFR Subpart E, 601.41 for biologics)
  - Fulfilled Phase 4 requirement with data from 2001 anthrax events

http://www.fda.gov/cder/drug/infopage/cipro/

Doxycycline / Penicillin G Procaine

- Already approved for anthrax
- FR Notice November 2, 2001 (p 55679)
  - Prescription Drug Products; Doxycycline and Penicillin G Procaine Administration for Inhalational Anthrax (Post-Exposure)
  - Clarifying that the currently approved indications for doxycycline and penicillin G procaine drug products include use in cases of inhalational exposure to Bacillus anthracis (the bacterium that causes anthrax).

Doxycycline / Penicillin G Procaine

- FR Notice (cont)
  - Providing dosing regimens determined to be appropriate for these products for this use.
    - Doxycycline 100 mg bid for adults; 1 mg/lb (2.2 mg/kg); PO or IV for 60 days.
    - Pen G procaine 1,200,000 units q12h in adults, 25,000 units/kg q12h in children
      - increased incidence of serum sickness-like reactions associated with use of penicillin for more than 2 weeks.

Drug Experience - Levofloxacin

- Relevant background information
  - FQ antimicrobial
  - Marketed since 1996
  - Safety in millions of adults, maximum 28 days based on AWC studies
  - No safety data available for pediatric patients
  - Efficacy demonstrated in multiple indications

Levofloxacin (cont)

- Data for PEP
  - In vitro susceptibility
  - Clinical pharmacology
    - Non human primate
      - Rapid clearance of levofloxacin
      - Use of hollow fiber to model doses
      - Daily 15 mg/kg (0h), followed by 4 mg/kg (12h) x 30 days
  - Non human primate model

Levofloxacin - approval and labeling

- Approved for PEP on November 24, 2004
  - Efficacy based on extrapolation from NHP
    - Subpart H surrogate endpoint
    - 500 mg qd x 60 days*
  - Only enough for adult safety for 28 days, labeling reflects this information
    - *The safety of levofloxacin in adults for durations of therapy beyond 28 days has not been studied. Prolonged levofloxacin therapy in adults should only be used when the benefit outweighs the risk
  - No safety data for pediatric patients provided

http://www.fda.gov/cder/drug/infopage/levaquin/default.htm

Biologic Products, including Monoclonal antibodies

Biologic Products

- Similarities
  - Three-tiered regulatory framework (laws, regs, guidances)
  - Some statutes regulate both (e.g., FDCA)
  - IND regulations apply to both
  - Effectiveness standard applies to both
  - Labeling regulations apply to each
  - Multiple guidances apply to both

Biologic Products

- Differences
  - Marketing approval regulated by PHS Act
    - Requirement to show that product is “safe, pure, and potent.”
    - Licensure applies to product and manufacturing establishment
  - Specific biologic regulations (21 CFR Part 600 *et seq*.)
    - Manufacturing and facility requirements
    - Licensure application and review procedures
    - Post-licensure reporting and regulation

Monoclonal Antibodies

Points to Consider in Manufacture and Testing of Monoclonal Antibody Products for Human Use, CBER, February 28, 1997

Monoclonal Antibodies

- Before clinical testing
  - Manufacture/characterization of mAb
  - Product safety testing for serious/life-threatening diseases 21 CFR 312.34
  - Preclinical studies
    - Preclinical pharmacology/toxicology, pK/pD
    - Testing of cross-reactivity of mAb
      - in vitro
      - In vivo animal safety
  - Microbiology
    - In vitro toxin neutralization
    - In vivo (see Animal Rule)

Monoclonal Antibodies

- IND, 21 CFR 312
  - Phase 1 and Phase 2 testing
    - Clinical pharmacology first in man
      - Dose setting
      - Antibody titers, antigen titers
  - Immunogenicity
    - Monitor for development of HAMA, HACA, HAHA
    - Evaluate for clinical findings
      - IgE anaphylaxis (e.g., OKT3, Mylotarg)
      - Infusion reactions (e.g., Rituxan)
      - Serum sickness (e.g., Remicade)

Factors likely to influence Immunogenicity*

- Murine contant regions, V-region sequence, Human Ig allotypes, unusual glycosylation
- Method and/or frequency of administration, dosage of antibody
- Patient's disease status, immune status, and/or MHC haplotype
- Specificity of antibody, cell-surface or soluble antigen, formation of IC with antigen
- Complement activation by mAb, Fc receptor binding by antibody, inflammation and cytokine release

*Clark, M "antibody humanization:" Review Immunology Today 21(8)397-402.

Monoclonal Antibodies

- IND 21 CFR 312 lead to licensing under 21 CFR 600
- Phase 3, comparative clinical studies serve to support approval. Examples of approved mAb products:
  - Rheumatoid arthritis: Remicade, Humira
  - Asthma: Xolair
  - Transplantation: Simulect, OKT3, Zenapax
  - Multiple sclerosis: Tysabri
  - Crohn's disease: Remicade
  - NHL: Rituxan, Bexxar
  - CML: Campath
  - Colon cancer: Avastin, Erbitux
  - Breast cancer: Herceptin
  - ***RSV Synagis*** *(infectious disease)*

Adverse events – Boxed Warnings

- Infections
  - Tuberculosis
- Infusion reactions
- Anaphylaxis
- Hemorrhage
- Cytopenias
- Severe cutaneous reactions
- Hepatotoxicity
- PML
- CPA, sudden death
- Wound healing complications
- Tumor lysis syndrome

Bacterial Infectious diseases

- Emerging pathogens
- Agents of Bioterrorism
  - Anthrax
  - Plague
  - Tularemia
  - Etc
- When human studies are not ethical or feasible

Evidence needed to demonstrate effectiveness of New Drugs (or Biologics) when human efficacy studies are not ethical or feasible [Animal Rule]*

*FR May 31, 2002 p37988

Final Rule effective July 1, 2002

Animal Rule

- Subpart H_Approval of Biological Products When Human Efficacy Studies Are Not Ethical or Feasible
- 21 CFR 601.91
  - (1) There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product;
  - (2) The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans;
  - (3) The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity; and
  - (4) The data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans

*FR May 31, 2002 p37988; Final Rule effective July 1, 2002

Animal Rule

- Subpart H_Approval of Biological Products When Human Efficacy Studies Are Not Ethical or Feasible
- 21 CFR 601.91
  - Postmarketing studies
  - Approval with restrictions to safe use
    - (i) Distribution restricted to certain facilities or health care practitioners with special training or experience;
    - (ii) Distribution conditioned on the performance of specified medical procedures, including medical follow up; and
    - (iii) Distribution conditioned on specified recordkeeping requirements.
  - Information to be provided to patient recipients

*FR May 31, 2002 p37988; Final Rule effective July 1, 2002

Animal Rule

- "We have decided to eliminate the requirement that 'products would be expected to provide meaningful therapeutic benefits' to patients over existing treatments"
  - Anthrax 2001 events indicate need for wide range of therapeutic options
  - Allergies and other adverse events
  - Availability
  - [Resistance]

Monoclonal Antibodies

- Animal rule
  - "safety evaluation of products in not addressed under this rule"
  - "products evaluated for effectiveness under subpart I for part 314 and subpart H of 601 will be evaluated for safety under preexisting requirements for establishing the safety of new drug and biologic products."
    - Human volunteers
    - Some data (interaction between toxic substance and product) may not be available

Anthax – *Bacillus anthracis*

- Information from publicly available sources
  - Anthim™ mAb (ETI-204) to PA, Infection and Immunity 2005; 73(2):795-802 (Elusys)
  - Heteropolymer binds PA in vitro, presented at 5th international conference on anthrax, Nice, France (Elusys)
  - ABthrax™ (PAmAb) fully human mAb against PA in Phase 1 study in healthy volunteers, CID 2005;41:12-20. (HGS)
  - Valortim™ humanized ab to PA, presented at IDSA (Medarex and PharmAthene)

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Questions?

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